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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. [2004D-0188]: "Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans" (69 Federal Register 25130; May 5, 2004)

Dear Sir/Madam:

The following comments on the above-captioned *Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans* (Draft Guidance) are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures, and markets leading prescription medicines for humans and animals and many of the world's best-known consumer brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier, and more productive lives. The company has three business segments: health care, animal health and consumer health care. Our products are available in more than 150 countries.

Pfizer is committed to provide access to safe and effective medicines. As a consequence, we have made a major commitment to Risk Management for the safety of our products. The cornerstone of our approach is to understand the unique characteristics of each product and implement relevant Risk Management strategies in ways that improve patient benefit without unreasonably restricting access. Thus, we agree strongly with statements in the Draft Guidance that a Risk Minimization Action Plan (RiskMAP) should only be considered for a "small number of products" and that RiskMAPs should "be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients." Indeed, we agree with FDA's proposal to replace the term "Risk Management Program" with "Risk Minimization Action Plan" (RiskMAP) to clarify the concept of specific actions that go beyond routine risk assessment and risk minimization.

The Draft Guidance, one of three on Risk Management activities[1], provides guidance on the development, implementation, and evaluation of RiskMAPs. When finalized, we

[1] The Draft Guidance is a companion document to two others: *Draft Guidance for Industry on Premarketing Risk Assessment* (Docket No. 2004D-0187; 69 Federal Register 25130; May 5, 2004) and *Draft Guidance for Industry on Good Pharmacovigilance Practices and*

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anticipate that the guidance will help provide transparency of the Agency's policies and expectations regarding this important aspect of drug development, which encompasses the rare situations "when a product may pose an unusual type or level of risk." We commend the Agency for actively engaging stakeholders in the development of this guidance and for considering our earlier comments. Indeed, we strongly endorse the use of Concept Papers[1] by FDA to facilitate early dialogue on important issues and we encourage FDA to continue this practice in the future. We appreciate the present opportunity to provide new comments and reinforce some of our previous comments on Risk Minimization Action Plans.

We consider the Draft Guidance to be a significant improvement over the Concept Paper as a result of our input and that of other stakeholders. Indeed, Pfizer agrees with and supports most of the concepts outlined in the Draft Guidance, particularly the over-arching philosophy that the ultimate goal of Risk Management is to ensure effective processes for minimizing risk while preserving benefits of medical products. We agree that this is an iterative process that should occur over the entire lifecycle of a product, with differences in intensity based on accrued experience, and, because all risk cannot be predicted with certainty, safety evaluations may need to be refined as experience with the product evolves. We also agree with the statement that, "Many recommendations in this guidance are ***not*** intended to be generally applicable to all products, since "risk assessment and risk minimization activities are already being performed for innovator products."

We believe that Risk Management activities are a shared responsibility and should encompass a worldwide perspective. Thus, we endorse FDA's participation in Industry-Regulator consensus forums, such as the International Conference on Harmonization (ICH) and the Council for International Organizations of Medical Sciences (CIOMS), to maintain global consistency and harmonization on this important topic. The Draft Guidance includes a non-specific statement regarding international harmonization, with the completed ICH E1A and E3 guidelines given as examples. However, relevant and important international consensus work is ongoing, e.g., activities of the ICH E2E Expert Working Group (Pharmacovigilance Planning) and the CIOMS VI Working Group (Managing Safety Information from Clinical Trials of Medicinal Products); the work products of these groups are scheduled to be finalized in the near future. Therefore, we strongly urge FDA to fully consider the final ICH and CIOMS consensus documents before finalizing the guidance on premarketing risk assessment.[2] If any divergence from consensus agreements were contemplated, it would be important for FDA to provide the rationale for the divergence and also an FDA proposal for eventual international harmonization.

Pharmacoepidemiologic Assessment (Docket No. 2004D-0189; 69 Federal Register 25130; May 5, 2004). Each of the three documents, developed to meet FDA's PDUFA III Performance Goals, was preceded by a draft Concept Paper and these papers were discussed at Public Workshops on April 9-11, 2003 (Docket 02N-0528; 68 Federal Register 11120, March 7, 2003, and 68 Federal Register 25049, May 9, 2003).

[2] FDA published notice of availability of ICH E2E draft guidance (Pharmacovigilance Planning) on March 30, 2004 (69 Federal Register 16579); the ICH consensus process on this topic will result in a final guidance (ICH Step 4) in November 2004 at the earliest. The CIOMS VI Working Group plans to make their report available in late 2004 or early 2005. The FDA Performance Goals associated with PDUFA III indicate that final guidance for pre-marketing risk assessment will issue by October 2004, before the international consensus documents are available.

Despite broad agreement with the Draft Guidance and its companion documents[1], we have identified several areas that we would like to reinforce as FDA contemplates final guidance. Our general comments on these areas are:

- **International harmonization provides advantages**. Risk Management is a shared global responsibility and stakeholders should endeavor to avoid multiple strategies merely to serve local needs, which could result in fragmented Risk Management for a given product (NB: Within a harmonized approach, however, there should be enough built-in flexibility to accommodate the real needs of individual products and individual countries). To further this, care should be taken to incorporate consensus definitions and approaches, e.g., those developed by ICH and CIOMS, wherever possible to ensure the most efficient use of resources by Industry and by Regulators. Please see the point above regarding related documents and the timing of their availability: The Agency should strive to be consistent with the international consensus documents and finalize the guidance only after the ICH E2E guidance and the CIOMS VI report are finalized;
- **Consistency in terminology and its use are critical**. To maximize the benefits of Risk Management, it is important to have clear terminology and definitions and to use these terms consistently. This should be done at the global level and also within and across FDA guidance documents. We note several inconsistencies within the Draft Guidance and companion documents. For example, the term "signal" is used with different meanings. Also, the terms "Risk Minimization Action Plan" ("RiskMAP") and "Pharmacovigilance Plan" ("PVP") are not used consistently across the three guidances. It is important to clarify in final guidance that a RiskMAP is reserved for selected occasions; the definition of a PVP and the use of this term should be aligned with the nascent ICH agreement. Another example is "Pharmacovigilance Scope," which seems to be used throughout the text with a narrower definition than the definition that was initially provided. We suggest that the Agency review terminology in the documents for clarity and consistency;
- **Stakeholder dialogue is essential**. The use of Concept Papers and Public Workshops was welcome in this case and is a practice that should be continued by FDA when introducing important guidance. This encourages early involvement of stakeholders and we believe that it serves to enhance transparency and will improve the desired public health outcome. In the case of the Draft Guidance, we believe that relevant stakeholders should be involved in both the development of guidance and in the planning and implementation of actions for situations when a product may pose an unusual type or level of risk. Mechanisms should be established to ensure (a) Dialogue between the Agency, Sponsor, and others, when appropriate, and (b) Interaction within the Agency, e.g., Reviewing Divisions and the Office of Drug Safety. We believe that it would be appropriate to establish a schedule of opportunities for dialogue at various stages of a product's lifecycle. Collaborative discussion of strategy and interpretation of data should result in a common understanding of relevant issues. We believe that this will provide a platform for constructive interactions in the best interest of the public health and will minimize misunderstandings. Further, it should be emphasized that all data sources should be considered; no single source of data should be used in isolation;

- **Risk Management is a continuum**. We believe, along with FDA, that the concept of Risk Management should begin early in product development and evolve at each phase of development as additional information is accumulated. However, all products are not the same and the need for Risk Management activities should be considered on a product-by-product basis;
- **Consensus must be reached on tools and it must be acknowledged that novel tools may emerge**. Simplicity and flexibility are the cornerstones of appropriate tools. We agree with the statement in the Federal Register notice (69 Federal Register 25131; May 5, 2004) that sponsors should"give every consideration to using the least burdensome method to achieve the desired public health outcome." This should be re-stated in all three guidance documents. Tools must be considered on a case-by-case basis, and agreed between the agency and the sponsor as appropriate. Because Risk Management is an evolving field, novel tools may be developed in response to a specific need. Further, a clear distinction should be made between tools that should be used to characterize risk versus those that can be applied to manage risk. For example, a case control study that is conducted as part of a Post-Approval Commitment may be useful to learn more about a certain risk, but such a study should not be considered useful as a tool to *manage* risk;
- **A uniform approach to labeling is needed**. Prescribing Information should be evidence-based and standardized where possible, e.g., agreement should be reached on what information goes into each section of product labeling and standard criteria should be developed for **bolded**, *italicized*, and black box wording. We believe that this would facilitate product comparisons by prescribers;
- **Individual willingness to accept risk should be considered when balancing benefit with risk**. Allowance for individual variability in willingness to accept risk, whether due to the nature of the underlying illness or the nature of the individual patient, should be considered in reaching a final decision on approvability of a product for marketing. The approach in the Draft Guidance is primarily population-based rather than patient-based and, although we understand FDA's role and interest in the public health, we feel a strictly population-based approach could unnecessarily restrict access to certain medications; and
- **Good Guidance Practices are encouraged**. The Agency's expectations should be tied directly to FDA's current legal authority to regulate the safety of drugs. Namely, FDA's expectations for regulated companies' Risk Management activities should be tied directly – and exclusively – to whether these activities help to ensure that marketed drug and biologic products are safe; these activities should avoid redundant or ineffective activities, and should not set different standards from those expressed in other guidance documents, e.g., size of safety database.

In addition, we would like to emphasize the following points:

- **Most products will not require a RiskMAP**. The Agency's expectations regarding the majority of marketing applications, which will not require a proposal for a voluntary RiskMAP, should be addressed in the final guidance. We think that voluntary development of a Patient Package Insert (PPI), for

example, should ordinarily be considered a routine Risk Management activity and not qualify as a RiskMAP. This could be an important distinction in preserving access, as any drug with a PPI, if the PPI is considered a RiskMAP, could be perceived as "riskier" than a similar product that does not have a PPI. This could lead to the paradoxical situation in which a product with an enhanced level of information intended to communicate and minimize risks is perceived being riskier than a product without such information. See related comment, below;

- **RiskMAPs should not unintentionally prevent patient access to beneficial products.** We generally support most of the concepts embedded in the Draft Guidance, but we are concerned that adoption of a RiskMAP could have a negative impact on innovation, i.e., an unintended consequence of Risk Management activities could be to dampen investment in novel medicines if certain concepts in the Draft Guidance are applied in an inappropriate manner. Examples of such unintended consequences include requirements for pre-approval large simple safety studies that delay availability of new drug products, and RiskMAP programs that unintentionally prevent patient access to beneficial products. Indeed, burdensome RiskMAP requirements associated with a new product could re-direct prescribers or patients to an older product that has an established profile, but the established product could actually have less potential benefit or more potential risk than the newer product. Furthermore, it should be made clear in the final guidance document that every attempt should be made to prevent the existence of a RiskMAP from jeopardizing patient access to newer products. We recommend that FDA and the sponsor continue a dialogue on this issue to ensure understanding of the RiskMAP by the public and the healthcare community. A product with a RiskMAP should not be perceived as riskier than one without a RiskMAP;
- **Triggers for RiskMAPs must be determined on a case-by-case basis.** The Draft Guidance states that the FDA may recommend consideration of a RiskMAP based on the "Agency's own interpretation of risk information." Expectations and transparency in this regard are very important; consistent standards and criteria should be used across all review divisions so that emphasis on evidence-based decision-making is maintained. To this end, FDA is specifically soliciting public comment on "how to best characterize the types and levels of risk that might suggest the need for a risk management plan." We believe that, rather than focus on when a risk management plan should be considered, FDA should establish expectations on when a RiskMAP should be considered. Both benefits and risks are "patient-specific and are influenced by such factors as the severity of the disease being studied, its outcome if untreated, existing therapeutic options, and the intended patient populations." These factors complicate assessment and comparison of pertinent data and this, in turn, is complicated by individual factors regarding perceptions of benefit and risk and individual willingness to accept risk for potential benefit. Because of the complicated nature of these factors, we do not believe that it is possible to create a standard formula that defines the types and levels of risk that might lead to a RiskMAP. However, we believe a general guideline for considering a RiskMAP should include at least the following criteria:

- Risks being considered should be established rather than hypothetical risk(s); and
- A beneficial impact on specific risk(s) can be anticipated from application of the RiskMAP.

Other criteria for considering a RiskMAP might include reasonable possibility that:

- Prescribers or patients or both would realize improved ability to make decisions regarding risk, e.g., the potential severity of a possible rare risk;
- A sub-population can be identified that may receive greater benefits of the drug but not might not otherwise have access to the drug; or
- The RiskMAP endpoint will be measurable and evaluable.

However, relevant stakeholders should collaborate to ensure that patient access to new effective therapy is not jeopardized by the existence of a RiskMAP and this should be made clear in final guidance. Application of these general criteria across all divisions should be monitored to ensure that RiskMAPs are not routinely considered for a large proportion of products and to ensure that products in the same/similar class with similar safety profiles meet risk minimization expectations in a uniform manner; and

- **RiskMAPs should not be open-ended**. We believe that specific actions implemented through RiskMAPs, and their results, should be monitored and brought to a conclusion when appropriate. The final guidance should indicate that there are circumstances, e.g., when the desired public health outcome has been achieved or certain target behaviors have been favorably modified, such that the sponsor might reduce intensity or otherwise scale back or discontinue elements of a RiskMAP. The guidance should specify that RiskMAPs are not to be considered an open-ended condition of marketing a specific product, but rather there are certain circumstances under which a RiskMAP should be modified or discontinued. In addition, final guidance should reflect the reality that RiskMAPs minimize, but do not completely eliminate, risk and few specific actions that require voluntary participation of healthcare providers will achieve 100% of their intended goal.

In summary, Pfizer endorses the thoughtful use of Risk Management concepts and practices throughout the continuum of a product's lifecycle, i.e., during the pre-approval, peri-approval, and post-marketing phases of product development. We believe that dialogue among stakeholders is key and we view Risk Management as a global process. In addition to population-based approaches, we place high importance on individual willingness to accept risk, whether due to the nature of the underlying illness or the nature of the individual patient, and this should be considered when making decisions regarding access to a given product. Harmonization of definitions, terminology, format, and tools will enable companies to use the same basic Risk Management Plan worldwide and enhance harmonization of Risk Management approaches around the globe for a specific product. We encourage FDA to strive for consistency with the relevant consensus documents from ICH and CIOMS, which may delay FDA's publication of final guidance because the consensus documents will not be available until after the PDUFA III Performance Goals date for the guidances.

Finally, we support comments made by the Pharmaceutical Research and Manufacturers Association (PhRMA) at the Public Workshops and we also support

PhRMA's written comments to Docket 02N-0528 and Docket 2004D-0188. We thank FDA for the opportunity to comment on this important topic and we would be pleased to respond to any questions that the Agency might have.

Our specific comments on the Draft Guidance are attached.

Sincerely,

Gretchen S. Dieck

Gretchen S. Dieck

cc: http:www.fda.gov/dockets/ecomments

Specific Comments

Development and Use of Risk Minimization Action Plans (Docket No. 2004D-0188)

These comments apply to the FDA Draft Guidance titled "Development and Use of Risk Minimization Action Plans," dated May 2004. Comments are arranged according to section of the Draft Guidance; each comment includes line references to the Draft Guidance where appropriate.

We acknowledge that FDA has addressed many of our previous specific comments. We have some lingering concerns in several areas:

Section: II.B. Overview of the Risk Management Draft Guidance Documents

We suggest that the sentence be revised to read: "(2) developing and implementing tools to minimize its risks while preserving or enhancing benefits to all or a subset of the target population." (lines 58-59)

We suggest that the following sentences be added to the end of this paragraph: "FDA explicitly recognizes that depending on personal preferences, disease, stage of disease and aggressiveness of the progression of the disease, some persons may wish to trade more risk for benefit. RiskMAPs can be used to enable that tradeoff by recognizing those preferences." (line 63)

With regard to the statement that the recommendations in this guidance focus on situations when a product may pose an unusual type or level of risk, we suggest that FDA clarify that the guidance applies only to those established risks, and not to hypothetical risks. For example, the recommendations should not be applicable for a product with limited safety information at the time of approval (i.e., it is unknown whether this product may pose an unusual level of risk). We also suggest that this sentence be revised to read: "... when a product may pose an unusual type or level of risk to all or a subset of the target population." (lines 76-77)

Reference is made to international harmonization efforts. We note that the draft ICH E2E guidance, which has also recently circulated for public comment, includes proposals for submission of Pharmacovigilance Specifications and Pharmacovigilance Plans. We suggest that the draft guidance for RiskMAPs and the draft Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment reflect how these FDA guidance documents correlate with the ICH E2E guidance. (lines 88-89)

Section: III. The Role of Risk Minimization and RiskMAPs in Risk Management

Since section C introduces the concept of a Risk Minimization Action Plan (RiskMAP), we suggest that this information precede the information presented

in section B.

We suggest that the first sentence in this paragraph be changed to: "...risk assessment, risk minimization, and/or benefit enhancement." (line 108)

We suggest that this sentence be changed to: "...while preserving or enhancing its benefits to all or a subset of the target population." (lines 112-113)

Section: III.A. Relationship Between a Product's Benefits and Risks

Discussion of the benefit-risk tradeoff appears very heavily weighted toward the "population" at risk and insufficiently targeted to the individual. The issue is more than simply a minimization of risks for the fixed benefits of the population at risk; many sub-groups and individuals would be willing to accept (trade off) more risk for benefit depending on personal preferences, disease, stage of disease and aggressiveness of the progression of the disease. That FDA recognizes this is somewhat intimated in lines 128-138 and lines 409-421; it bears repeating and stating explicitly throughout, though. Risk assessments and plans should enable the FDA to permit targeted indications to individuals for use of a treatment where risk is higher than that for the total population at risk, thereby enabling patients and their physicians to make more appropriate treatment choices. This is more than just minimization of risks for a given benefit; this is acknowledgment of individual preferences and rights for a trade-off. We suggest that a statement to this effect be added to the guidance document. (128-138)

With regard to the statement that risks and benefits are usually measured in different units, it should be mentioned that a number of methods that put benefits and risks of a drug product in the same context are under development (see additional comments related to lines 212-217). (lines 132-133)

Section: III.C. Definition of Risk Minimization Action Plans (RiskMAP)

The roles of pharmaceutical companies and the role of healthcare providers are different from one another. Pharmaceutical companies should and do strive to minimize risk to patients, but healthcare providers have a much more direct role in minimizing risk to individual patients; we do not believe that it is the responsibility of pharmaceutical companies to "police" healthcare providers or the practice of medicine. (lines 179-181)

Section: III.D. Determining When a RiskMAP Should be Considered

It is important to recognize the value of early dialog between Agency and the sponsor, which should be before a decision to implement Risk MAP is made. A reminder to that effect should be inserted as a prefatory statement to Section D. (line 193)

This note mentions that a generic product "...may have the same or similar benefit-risk balance as the innovator...." With the possible exception of brand

name confusion, generic products should, by definition, have an identical benefit-risk balance as the innovator. We request that FDA either clarify those situations where a generic product would not be identical to the innovator product or modify this statement accordingly. (line 193, footnote 6)

The document suggests that "nature and rate of known risks versus benefits" be considered when trying to determine if development of a RiskMAP is desirable. The need to compare benefits to risks is obvious, although we agree with the FDA that such an assessment is a very complicated process. To minimize bias in how the risks are weighted in light of benefits, it might be useful for the FDA to consider models as they make such assessments in the future. Currently, this benefit-risk assessment is basically a judgment call, and that is partially due to the fact that most models are not sophisticated enough to be useful or have not been validated. While that is still the case, more work is being done with respect to evaluating such models. Exploring the use of models such as these might be considered as a way to help bring consistent thinking into the FDA review process concerning the balance of benefits and risks for drug products throughout their life cycle. A more rigorous approach may help to ensure that the assessment is not influenced, for example, by placing an inordinate emphasis on a very rare risk or on merely theoretical risks, and that the assessment is actually more balanced. (lines 212-217)

We also suggest that "preferences of the population at risk for both benefits and risk in the context of their medical situation" be added as a fifth characteristic to be weighed. (line 217)

As indicated above, defining specific criteria that would trigger consideration of a RiskMAP is challenging. The example of Schedule II controlled substances is important, but rather than single this group out as an example of when a RiskMAP should *always* be considered, we suggest replacing the example with an additional bullet: "there is significant risk-associated abuse and product diversion." (lines 225-228)

Section: IV. Tools for Achieving RiskMAP Goals and Objectives

When discussing various tools for risk management it is important to keep in mind that there may be an opportunity to learn and share various experiences. We salute Agency's plans to make tools available and transparent, to a certain level. These may serve as learning opportunity and help various companies to avoid mistakes and apply successfully new learning. (line 230)

Section: IV.C Description of RiskMAP Tools

We support an FDA web site that summarizes contemporary experience with risk tools consistent with federal laws and regulations governing disclosure of information to the public. However, as mentioned in our general comments above, we believe that the web site should also contain FDA's analyses of previous plans and the tools used, including overall feasibility assessments, as well as the known advantages, disadvantages, and limitations associated with a given tool. (lines 345-354)

Section: V.A. Rationale for RiskMAP Evaluation

There is an apparent contradiction between the statement in lines 469-471 ("Statistical hypothesis testing would not typically be expected, given the limitations of the data likely to be available") and a later statement in lines 817-819 ("measurement errors, sensitivity, specificity, as well as power and confidence intervals where appropriate"). This later statement implies that the data will have more rigor than is generally expected. We request that FDA clarify this seeming contradiction. (lines 469-471)

Section: V.B. Considerations in Designing a RiskMAP Evaluation Plan

RiskMAP evaluation plans are "...designed to assess whether the RiskMAP's goals have been achieved through its objectives and tools." However, most goals will not be 100% achievable because of human fallibility and the FDA's acknowledged lack of jurisdiction over physician's prescribing or medical practice. This limitation should be acknowledged or described in the guidance document. (lines 476-477)

RiskMAPs should seek continuous improvement until an acceptable risk-benefit balance is maintained. Specific quantitative reporting goals are particularly problematic as are *a priori* thresholds for action. Refinements of a RiskMAP require an assessment of the quantity and quality of reports, nature and severity of events that occur after the interventions have had time to make an impact. The decision to add, modify or remove tools requires a comprehensive assessment of all available information rather than focus on an isolated metric. (lines 482-508)

If the final guidance retains the requirement for specific quantitative goals, it is imperative that the agency provides guidance on the criteria to be used for goal setting. A specified number or rate of a complication may not be established at time of initiation of RiskMAP. For example, if a drug is the first in the class and/or the background rate of the adverse event of interest has not been studied, especially within the RiskMAP environment, it would be difficult to define the threshold. (lines 486-488)

We suggest that this sentence be changed to: "...than a specified number or rate of that complication, or improving the outcome of the adverse event." (line 488)

The Draft Guidance states that if health outcomes cannot be practically or accurately measured, closely related measures can be used. We request that FDA acknowledge that it might take significant time and resource to accumulate enough meaningful data to demonstrate that rates of an event have subsided and by how much. We request additional discussion on the decision-making process that would lead to the choice of monitoring an actual patient outcome versus a closely related measure. (lines 488-508)

Spontaneous AE data are described as "potentially" biased outcome measures. We suggest that this be corrected to say that spontaneous report data are "inherently biased outcome measures..." (lines 516-518)

This section appears to suggest that claims databases do not include patients of lower socioeconomic status. However, Medicaid claims databases have data on medical care to some categories of economically disadvantaged and disabled persons. In addition, because of the infrastructure of the European health care system, many European pharmacoepidemiologic databases include a sample of all patient groups, irrespective of socioeconomic status. (lines 522-530)

The Draft Guidance discusses the potential for an evaluation of a RiskMAP to allow the opportunity to discontinue a tool if the individual tool is performing poorly. While poorly performing tools should be discontinued, we would also like to see the acknowledgement that it might be appropriate to discontinue a tool if it proved to be successful and, therefore, was no longer needed, or if there were another redundant tool which superceded the need for the tool. (lines 568-571)

We request clarification regarding the tools for which sponsors would be expected to perform pre-testing in a clinical trial setting such as a large simple safety study. Including testing of tools in clinical trials would add a layer of complexity to both the performance and analysis of the trials and could possibly lead to an increase in the sample size required to assure adequate population of analytical cells. (line 590)

Section: V.C. FDA Assessment of RiskMAP Evaluation Results

In the spirit of transparency and maximizing impact on the public health, we recommend that FDA share the results of its assessment of the RiskMAP effectiveness with the sponsor/applicant and discuss any differences of interpretation (reference line 652). (lines 611-613)

Section: VI. Communicating with FDA Regarding RiskMAP Development and Design Issues

To initiate a dialog with FDA regarding the Agency's experience with previously implemented RiskMAPs, it would seem logical for a sponsor/applicant to also be able to contact the Office of Drug Safety, as they would have experience with a broader range of products and RiskMAPs than a single review division. We suggest revising the end of this sentence to read: "...contact the product's review division for product-specific risk management issues, or the Office of Drug Safety for information on FDA's general experience with risk management tools." (lines 645-646)

Section: VII.A. Contents of a RiskMAP Submission to FDA

In this section, we agree with the Agency's emphasis on what should be submitted to FDA in those instances when a RiskMAP is needed. However, as noted in our general comments above, we feel that the Agency should also address its expectations pertinent to the content/format issues related to risk management information to be included in marketing applications for the

majority of drugs that do not warrant a RiskMAP. (line 679)

This bullet should add language to clarify that RiskMAP modification can be in either direction; new tools can be added, but tools can also be removed, or the RiskMAP terminated altogether. (lines 770-773)

We recommend that the Agency reconsider expecting milestones and written progress reports for all RiskMAPs. Instead, constructive dialog and information exchange between FDA and the sponsor should be based on the circumstances of the particular product. (line 779)

If the requirement for written progress reports is retained in the final guidance document, we suggest that the sentence be changed to read: "FDA recommends progress reports be included in the Periodic Safety Reports (PSURs) or traditional Periodic Reports, or submitted at the same time as the sponsor submits these reports." (lines 783-784)

Section: VII.B. Contents of a RiskMAP Progress Report

We request that FDA clarify what measurement errors, sensitivity, etc. are being referred to in this paragraph. (lines 817-818)

The proposed guidance states that a sponsor might choose to propose modifications to the RiskMAP "if the RiskMAP goals were not achieved." As indicated in our comments regarding lines 770-773, we believe that modifications to RiskMAPs can and should occur in either directions, as might be appropriate for the situation. (838-839)